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1. Cancer Biotherapy & Radiopharmaceuticals, 2000, 15(1):71-79

2. Cancer Research, 2002, 62(15):4263-4272

3. Women's Oncology Review, 2002, 2(4):411-412

4. CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:951264 CAPLUS
DOCUMENT NUMBER: 139:272943
TITLE: Direct electrophilic radiofluorination of a cyclic RGD peptide for in vivo .alpha.v.beta.3 integrin related tumor imaging
AUTHOR(S): Ogawa, Mikako; Hatano, Kentaro; Oishi, Shinya; Kawasumi, Yasuhiro; Fujii, Nobutaka; Kawaguchi, Michiya; Doi, Ryuichiro; Imamura, Masayuki; Yamamoto, Mikio; Ajito, Keiichi; Mukai, Takahiro; Saji, Hideo; Ito, Kengo
CORPORATE SOURCE: Department of Biofunctional Research, National Institute for Longevity Sciences, Gengo, Morioka-cho, Obu, 474-8522, Japan
SOURCE: Nuclear Medicine and Biology (2002), Volume Date 2003, 30(1), 1-9
CODEN: NMBIEO; ISSN: 0969-8051
PUBLISHER: Elsevier Science Inc.
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5. CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:894626 CAPLUS
DOCUMENT NUMBER: 135:89216
TITLE: Recent progress in the field of .alpha.v-integrin antagonists
AUTHOR(S): Kessler, Horst; Kantlehner, Martin; Gibson, Christoph; Haubner, Roland; Finsinger, Dirk; Dechantsreiter, Michael; Planker, Eckart; Wermuth, Jochen; Schmitt, Jorg S.; Meyer, Jorg; Schaffner, Patricia; Holzemann, Gunter; Wiesner, Matthias; Goodman, Simon L.; Hahn, Diane; Jonczyk, Alfred; Wester, Hans J.; Schwaiger, Markus
CORPORATE SOURCE: Institut fur Organische Chemie und Biochemie, Technische Universitat Munchen, Garching, 85747, Germany
SOURCE: Peptides for the New Millennium, Proceedings of the American Peptide Symposium, 16th, Minneapolis, MN, United States, June 26-July 1, 1999 (2000), Meeting Date 1999, 235-237. Editor(s): Fields, Gregg B.; Tam, James P.; Barany, George. Kluwer Academic Publishers: Dordrecht, Neth.
CODEN: 69ATHX
DOCUMENT TYPE: Conference
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REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS

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Women's Oncol Rev 2002;2:411–12

Critical Commentary
Basic Sciences

Cilengitide targeting of $\alpha_v\beta_3$ integrin receptor synergizes with radioimmunotherapy to increase efficacy and apoptosis in breast cancer xenografts

Burke PA, DeNardo SJ, Miers LA, Lamborn KR, Matzku S, DeNardo GL. *Cancer Res* 2002;62:4263–72

Commentary by: Emanuela Ghia, 'La Sapienza' University, Rome, Italy, and Giuseppina D'Andrilli, BS, Sbarro Institute for Cancer Research and Molecular Medicine, College of Science and Technology, Temple University, Philadelphia, PA

Objective:

To evaluate the efficacy of the cyclic Arg-Gly-Asp peptide Cilengitide combined with systemic radioimmunotherapy (RIT) in human breast cancer tumor models.

Introduction:

Systemic, tumor-targeted RIT has the potential to target tissue specifically and to deliver cancer-specific cytotoxic antibodies to widespread metastatic foci; however, studies in human breast cancer xenograft models demonstrate that RIT, as a single agent, typically does not cure the tumors. New and synergistic therapeutic combinations are required for the treatment of metastatic breast cancer, which is currently incurable with standard multimodality therapy. The combination of antiangiogenic agents, such as Cilengitide, with RIT is a novel approach in which two agents act against distinct compartments within tumors: antiangiogenic agents suppress the endothelial compartment, whereas RIT acts directly on the tumor cell. Synergy of RIT with other antiangiogenic or chemotherapeutic agents has been demonstrated in several tumor models. The particular appeal of antiangiogenic agents is their potential to target a non-resistant population of cells without increased toxicity, making antiangiogenic agents promising for chronic therapy to prevent tumor cell recovery and metastasis. The combination of the antiangiogenic agent Cilengitide with RIT significantly increased efficacy, inducing apoptosis in endothelial cancer cells without apparent increased toxicity.

Methods:

- Injection of HBT 3477 (human breast adenocarcinoma cell line expressing the *bcl-2* gene and containing a p53 mutation) into III female mice.
- During 84 days, 24 mice received no treatment, 46 mice received RIT as a single agent and 41 mice received RIT combined with Cilengitide in six doses of 250 mg.
- TUNEL analysis was used to evaluate the rate of apoptotic cells.
- An OLYMPUS microscope was used to determine the average number of proliferating cells and the average microvessel density.

Results:

- RIT combined with Cilengitide resulted in significantly more cures (44% cure rate) than RIT (20% cure rate).
- Cilengitide, administered alone or in combination with RIT, did not significantly increase toxicity.
- Apoptosis in total and endothelial cells after RIT combined with Cilengitide was higher than in all of the other treatment groups at almost all time points.
- RIT combined with Cilengitide decreased cell proliferation compared to untreated mice and resulted in significantly decreased proliferation at 6 days compared to RIT alone.
- Significantly decreased microvessel density compared to untreated mice was observed 6 days after RIT in mice receiving either RIT alone or combined with Cilengitide.

Conclusions:

These results indicate that significantly better outcome of therapy is associated with RIT combined with Cilengitide, compared to therapy with a single agent, without an accompanying statistical increase in toxicity.

Selected references:

Burke PA, DeNardo SJ, Miers LA, *et al.* Combined modality radioimmunotherapy: promise and peril. *Clin Cancer Res* 2002;94:1320–31

Bruce NG, Kramer E, Liebes L, *et al.* Radiosensitization of tumor-targered radioimmunotherapy with prolonged topotecan infusion in human breast cancer xenografts. *Cancer Res* 2001;61:2996–3001

DeNardo SJ, Kukis DL, Kroger LA, *et al.* Synergy of Taxol and radioimmunotherapy with yttrium-90-labeled chimeric L6 antibody: efficacy and toxicity in breast cancer xenografts. *Proc Natl Acad Sci USA* 1997;94:4000–4

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MacDonald TJ, Taga T, Shimada H, *et al.* Preferential susceptibility of brain tumors to the antiangiogenic effects of v integrin antagonist. *Neurosurgery* 2001;48:151–7
Mitjans F, Meyer T, Fittschen C, *et al.* In vivo therapy of malignant melanoma by means of antagonists of v integrins. *Int J Cancer* 2000;87:716–23

Commentary:

This article imparts a novel twist to the synergistic therapeutic combinations for the treatment of metastatic breast cancer, by demonstrating that combining Cilengitide and RIT achieved an increase in the efficacy of therapy without additional toxicity. In particular, the therapeutic synergy is likely to be caused by the combined effects of several mechanisms, leading to increased apoptosis and decreased proliferation because cyclic Arg-Gly-Asp peptides, such as Cilengitide or RGDf-ACHA, target and block the $\alpha_v\beta_3$ receptor, thus inducing apoptosis in endothelial cells, inhibiting angiogenesis and blocking tumor growth. Much work is needed to investigate why a clear pattern of endothelial apoptosis is not preceding total cell apoptosis and why the increased endothelial apoptosis, associated with RIT in combination with Cilengitide treatment, did not appear to be associated with measurable differences in microvessel density. As the authors suggest, these data indicate that increased endothelial apoptosis observed with RIT combined with Cilengitide treatment may contribute to, but is not likely to be the only mechanism affecting, the therapeutic outcome.

Cilengitide is currently used in clinical trials (phase I/II for anaplastic glioma and phase I for Kaposi's sarcoma) with only mild side-effects, including nausea, anorexia, fatigue and malaise, with no bone marrow suppression and no dose-limiting toxicity.

The combination of the antiangiogenic agent Cilengitide with RIT is not the only combined treatment tested in human cancer; recently another antiangiogenic agent, thalidomide, combined with RIT has been tested in the treatment of xenografts of human colon cancer cells. Thalidomide possesses potent antiangiogenic properties, which arise as a result of blockade of the action of angiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).

Although the combination of RIT and thalidomide therapy is significantly associated with a decreased microvessel density, thalidomide displays several adverse effects, including somnolence, constipation, skin rashes, orthostatic hypotension, nausea, peripheral neuropathy and neutropenia; therefore, it has to be established whether this combined therapy increases myelotoxicity in animals.

In conclusion, the remarkable peculiarity of this paper is the enhanced therapeutic response achieved by adding the antiangiogenic agent Cilengitide to RIT without increased toxicity; which indicates immense potential specifically for Cilengitide, the first antiangiogenic agent that does not add toxicity when used in therapeutic combination with RIT.

Further reading:

DeNardo SJ, O'Donnell RT, Kroger LA, *et al.* Strategies for developing effective radioimmunotherapy for solid tumors. *Clin Cancer Res* 1999;10:3219–23
Kinuya S, Kawashima A, Yokoyama K, *et al.* Cooperative effect of radioimmunotherapy and antiangiogenic therapy with thalidomide in human cancer xenografts. *J Nucl Med* 2002;43:1084–9
Vogel CA, Galmiche MC, Buchhegger F. Radioimmunotherapy and fractioned radiotherapy of human colon cancer liver metastases in nude mice. *Cancer Res* 1997;57:447–53
Wei BR, Ghetie MA, Vitetta ES, *et al.* The combined use of an immunotoxin and a radioimmunoconjugate to treat disseminated human B-cell lymphoma in immunodeficient mice. *Clin Cancer Res* 2000;6:631–42

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